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RESEARCH ARTICLE

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Impact of microvascular invasion on clinical outcomes after curative-intent resection for intrahepatic cholangiocarcinoma

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Background: Microvascular invasion (MiVI) is a histological feature of intrahepatic cholangiocarcinoma (ICC) that may be associated with biological behavior. We sought to investigate the impact of MiVI on long-term survival of patients undergoing curative-intent resection for ICC.

Methods: A total of 1089 patients undergoing curative-intent resection for ICC were identified. Data on clinicopathological characteristics, disease-free survival (DFS), and overall survival (OS) were compared among patients with no vascular invasion (NoVI), MiVI, and macrovascular invasion (MaVI).

Results: A total of 249 (22.9%) patients had MiVI, while 149 (13.7%) patients had MaVI (±MiVI). MiVI was associated with higher incidence of perineural, biliary and adjacent organ invasion, and satellite lesions (all $P < 0.01$). On multivariable analysis, MiVI was an independent risk factor of DFS (hazard ratios [HR] 1.5; 95%confidence intervals [CI], 1.3-1.9; $P < 0.001$), but not OS (HR 1.1; 95%CI, 0.9-1.3; $P = 0.379$). While MiVI and MaVI patients had similar DFS (median, MiVI 14.0 vs MaVI 12.0 months, HR 0.9; 95%CI, 0.7-1.2; $P = 0.377$), OS was better among MiVI patients

(median, MiVI 39.0 vs MaVI 21.0 months, HR 0.7; 95%CI, 0.5-0.8; $P = 0.002$). Whereas nodal metastasis, R1 margin, and postoperative morbidity were associated with early death (≤18 months) among patients with MiVI, only nodal metastasis was associated with late (>18 months) prognosis.

Conclusions: Roughly 1 out of 5 patients with resected ICC had MiVI. MiVI was associated with advanced tumor characteristics and a higher risk of tumor recurrence.

KEYWORDS

intrahepatic cholangiocarcinoma (ICC), macrovascular invasion (MaVI), microvascular invasion (MiVI), prognosis

1 | INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is the second most common primary liver tumor after hepatocellular carcinoma (HCC), and its incidence and mortality are increasing worldwide.[1,2] Surgical resection is currently the only potentially curative treatment option for patients with ICC.[3] However, long-term survival after curative resection among patients with ICC is disappointing. Specifically, 5-year survival after resection has been reported to be only 20%-35% with over two-thirds of patients experiencing recurrence.[4-6]

The vascular invasion has been identified as one of the strongest risk factors contributing to recurrence and death of patients with ICC after surgery.[7,8] The 7th and 8th editions of the American Joint Committee on Cancer (AJCC) staging manual incorporate vascular invasion within the T category designation.[9] Macrovascular invasion (MaVI) is defined as tumor invasion into a major vessel that can be identified by radiological imaging or macroscopic examination. In contrast, the diagnosis of microvascular invasion (MiVI) is largely dependent on histological examination.[10] Generally, MiVi has been defined as the presence of tumor emboli in a portal radical vein, large capsule vessel, or in a vascular space lined by endothelial cells.[10] MiVI has been extensively studied and reported to be a strong indicator of worse outcomes among patients with hepatocellular carcinoma (HCC) after resection or liver transplantation.[10-17] In fact, MiVI is now recognized as the main cause of MaVI and intrahepatic metastasis among patients with HCC.[18] In turn, HCC with histologically confirmed MiVI have a high risk of recurrence after resection and several studies have suggested that adjuvant therapies, such as transarterial chemotherapy and embolization[19,20] and sorafenib,[21] may improve the outcome of these patients. In contrast, the potential impact of MiVI on the long-term outcome of patients with ICC has not been well investigated. As such, the objective of the present study was to define the clinical impact of MiVI on the prognosis of patients after curative-intent resection of ICC using a large, multi-institutional, international database.

2 | PATIENTS AND METHODS

2.1 | Study cohort

Patients undergoing resection with curative intent for ICC from 1990 to 2015 were collected from a multi-institutional database that included 14 major hepatobiliary centers in the USA, Europe, Australia, and Asia (The Ohio State University, Columbus, Ohio; Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University Medical Center, Stanford, California; University of Virginia Health System, Charlottesville, Virginia and Ottawa General Hospital, Ottawa, Canada, Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Yokohama City University, Yokohama, Japan; Royal Prince Alfred Hospital, Sydney, Australia; Fundeni Clinical Institute, Bucharest, Romania; Beaujon Hospital, Clichy, France; Curry Cabral Hospital, Lisbon, Portugal; San Raffaele Hospital, Milan, Italy; and Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands). The diagnosis of ICC was histologically confirmed in all cases. Resection with curative intent was defined as macroscopic removal of all tumors (R0 or R1 resection). Patients who underwent palliative or R2 resection, ablation, or intra-arterial therapy and patients with extrahepatic metastasis were excluded. The Institutional Review Boards of each participating institution approved the study.

2.2 | Data collection and follow-up

Preoperative variables, including standard demographic, clinicopathological, and tumor-related characteristics, were collected using a standardized data sheet. All resected specimens were subjected to histological analysis and were evaluated for tumor size, number, morphology, differentiation, margin, vascular, biliary and perineural invasion, lymph node status, as well as adjacent organ invasion. MaVI was defined as invasion of the tumor into a major vessel that was identified during the macroscopic examination or radiographic imaging; MiVI was defined as tumor invasion of hepatic veins, portal system, and lymphatic ducts that were visible only on microscopy.[10,15]

An R0 resection was defined as a minimum margin length of >1 mm; the microscopic presence of tumor at the margin or a minimum margin length of ≤1 mm was designated as an R1 resection. Pathologic staging was assigned according to the 8th edition American Joint Committee on Cancer (AJCC) staging guidelines.[9] Details of the operation were documented and collected, including resection mode, lymphadenectomy, operation time, and intraoperative blood loss.

After discharge, all patients were regularly followed with serum carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), and imaging studies, including abdominal ultrasonography, computed tomography and/or magnetic resonance imaging (MRI) until the death of the patient or the end of the study. In the present study, the primary endpoints were overall survival (OS) and disease-free survival (DFS). OS was defined as the time duration from the date of initial resection to patient death or the end of the study. DFS was defined as the time duration from the date of initial surgery to tumor recurrence. Recurrence was defined as suspicious imaging findings or biopsy-proven tumor. The site of recurrence was categorized as intrahepatic and/or extrahepatic. Treatments of recurrence were tailored according to the tumor burden and general condition of the patient. Curative-intent therapies for recurrence included surgical re-resection, ablation, or combined resection plus ablation.

2.3 | Statistical analysis

Continuous variables were expressed as medians with interquartile ranges; student *t* test or the Mann-Whitney *U* test were used for statistical analysis as appropriate. Categorical variables were expressed as number and percentages and compared with χ^2 test or Fisher's exact test. Survival was analyzed by the life table and Kaplan-Meier method and compared with the logrank test. Factors associated with OS and DFS were identified using univariate and multivariable Cox proportional hazards regression models. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated. The variables with a *P* value less than 0.05 on univariate analysis were included in the multivariable models. A two-tailed *P* value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 21.0 (IBM SPSS Inc, Chicago, IL).

3 | RESULTS

3.1 | Baseline characteristics

Among 1,089 patients who underwent curative-intent resection for ICC, 149 (13.7%) had MaVI with or without MiVI, while 249 (22.9%) had MiVI on histological examination without evidence of MaVI. The clinicopathological characteristics and surgery details among patients with no vascular invasion (NoVI) vs MiVI vs MaVI were compared (Table 1). Although tumor size and number, as well as serum markers (ie Ca19-9 and CEA) were not different among the three groups, tumors with either macro- or MiVI had a higher incidence of perineural, biliary and adjacent organ invasion, as well as the presence of satellite lesions (all $P < 0.01$). In addition, patients with vascular invasion were more likely to have advanced AJCC T disease, lymph node metastasis, and poor tumor differentiation vs patients with NoVI (all $P < 0.05$). Although patients with macro- or MiVI were more likely to undergo a major hepatectomy and concomitant lymphadenectomy (both $P < 0.01$), the incidence of an R0 resection was lower among patients with vs without vascular invasion (MaVI 79.2%, MiVI 80.3% vs NoVI 92.0%; $P < 0.001$). Among patients who had the vascular invasion, patients with MaVI had a higher incidence of adjacent organ invasion (13.4% vs 5.6%), nodal metastasis (37.7% vs 22.9%) compared with patients who had MiVI (all $P < 0.05$). In contrast, tumor size, number, as well as the incidence of the perineural and biliary invasion were equivalent among patients with MaVI vs MiVI. The frequency of adjuvant chemo- and radiotherapy was comparable among patients with MiVI and MaVI; of note, the use of chemotherapy among these patients was higher than patients without vascular invasion (MiVI 38.3%, MaVI 39.8% vs NoVI 24.7%; $P < 0.001$).

3.2 | Survival of patients stratified by vascular invasion

After a median follow-up of 35 (range 3-211) months, a total of 553 (50.8%) patients had died. In examining the entire cohort, 1-, 3- and 5-year OS was 78.8%, 49.9%, and 38.7%, respectively, while 1-, 3- and 5-year DFS was 57.4%, 35.2% and 19.5%, respectively. Of note, patients with MiVI had a better OS compared with patients who had MaVI (median OS, MiVI 39.0 vs MaVI 21.0 months; HR 0.7; 95%CI, 0.5-0.8; $P = 0.002$), which was comparable with patients who had NoVI (median OS, MiVI 39.0 vs NoVI 45.0 months; HR 1.2; 95% CI, 0.9-1.5; $P = 0.194$) (Figure 1A). In contrast, patients with MiVI had a similar DFS as patients with MaVI (median DFS, MiVI 14.0 vs MaVI 12.0 months, HR 0.9; 95% CI, 0.7-1.2; $P = 0.377$), which was worse than patients with NoVI (median DFS, MiVI 14.0 vs NoVI 21.0 months, HR 1.5; 95%CI 1.3-1.9; $P < 0.001$) (Figure 1B).

On multivariable analysis, after taking into account competing risk factors, MaVI (HR 1.5; 95%CI, 1.1-1.9; $P = 0.005$), rather than MiVI (HR 1.1; 95%CI, 0.9-1.3; $P = 0.379$), was associated with worse long-term survival (Table 2). In contrast, both MaVI (HR 1.4; 95%CI, 1.0-1.8; $P = 0.022$) and MiVI (HR 1.6; 95%CI, 1.3-2.0; $P < 0.001$), tumor size, number, and differentiation, as well as lymph node status were correlated with risk of tumor recurrence (Table 3).

3.3 | Recurrence and treatments

During follow-up, 729 (66.9%) patients experienced tumor recurrence after surgery. Among patients who recurred, patients with MaVI or MiVI were more likely to develop extrahepatic recurrence than patients with NoVI (MaVI 42.2%, MiVI 41.8% vs NoVI 31.6%; $P = 0.003$) (Figure 2A). The recurrence pattern was similar among patients with MiVI vs MaVI (Figure 2A). Among 626 patients who were treated for recurrence, patients with MiVI were more likely to undergo a subsequent curative-intent treatment compared with patients with MaVI (17.7% vs 7.0%; $P = 0.033$). The utilization of repeat curative-intent treatments for recurrences was similar among patients with NoVI and MiVI who recurred (17.7% vs 12.1%; $P = 0.082$) (Figure 2B). Perhaps not

TABLE 1 Clinicopathological characteristics and surgical treatments of patients undergoing curative resection for intrahepatic cholangiocarcinoma stratified by vascular invasion status

	No vascular invasion (n = 691)	Microvascular invasion (n = 249)	Macrovascular invasion (n = 149)	*P* value
Age, y	59 (50-66)	63 (54-71)	62 (52-71)	<0.001
Male gender	391 (57.5%)	132 (53.0%)	81 (54.4%)	0.422
Body mass index, kg/m^2	25.3 (22.4-28.0)	24.8 (22.6-28.4)	24.6 (21.2-27.0)	0.183
Carbohydrate antigen 19-9, U/mL	43.5 (15.1-180.2)	60.0 (20.0-239.3)	60.9 (22.8-382.0)	0.515
Carcinoembryonic antigen, ng/mL	2.4 (1.5-4.0)	2.4 (1.4-4.4)	2.4 (1.2-6.0)	0.800
Tumor size, cm	6.0 (4.0-8.0)	7.0 (4.5-9.1)	6.5 (4.5-9.0)	0.805
Multiple lesions (≥2)	108 (15.6%)	42 (16.9%)	22 (14.8%)	0.412
Perineural invasion	55 (8.0%)	81 (32.5%)	63(42.3%)	<0.001
Direct invasion of adjacent organs	43 (6.2%)	12 (5.6%)	20 (13.4%)	<0.001*
Biliary invasion	42 (6.1%)	51 (20.5%)	39 (26.2%)	<0.001
Satellite lesions	123 (17.8%)	72 (28.9%)	47 (31.5%)	<0.001
AJCC T stage				<0.001
T1–2	578 (83.6%)	117 (47.0%)	61 (40.9%)	
T3–4	64 (9.3%)	58 (23.3%)	44 (29.6%)	
Missing	49 (7.1%)	74 (29.7%)	44 (29.5%)	
AJCC N status				<0.001*
N0	407 (61.2%)	94 (42.2%)	47 (44.3%)	
N1–2	79 (11.9%)	51 (22.9%)	40 (37.7%)	
Nx	179 (26.9%)	31 (35.0%)	19 (17.9%)	
Histological grade				0.007
Well/ moderately differentiated	548 (79.3%)	162 (65.1%)	83 (55.7%)	
Poorly to undifferentiated	94 (13.6%)	50 (20.1%)	22 (14.8%)	
Missing	49 (7.1%)	37 (14.9%)	44 (29.5%)	
R0 resection	636 (92.0%)	200 (80.3%)	118 (79.2%)	<0.001
Major resection (≥3 segments)	139 (20.1%)	101 (40.6%)	87 (58.4%)	<0.001*
Lymphadenectomy	242 (35.0%)	149 (59.8%)	71 (47.7%)	<0.001
Intraoperative blood loss, mL	300 (200-600)	525 (300-1006)	800 (500-1200)	0.002
Operation time, min	174 (108-254)	310(210-436)	301 (180-640)	0.474
Postoperative morbidity	228 (33.0%)	106 (42.6%)	55 (36.9%)	<0.001
Adjuvant chemo- and radiotherapy	171 (24.7%)	99 (39.8%)	57 (38.3%)	<0.001

Abbreviation: AJCC, American Joint Committee on Cancer.
*indicates a *P* value less than 0.05 when compared between microvascular and macrovascular invasion groups.

surprisingly, median OS after the first recurrence among patients with MaVI (8.0 months) was worse than patients with MiVI (17.0 months) or NoVI (13.0 months) ($P < 0.001$).

3.4 | Survival of patients with MiVI: Early death versus long-term survival

In examining OS of patients with MiVI vs MaVI, long-term survival was initially generally similar, yet became divergent beginning roughly around 18 months after surgery (cumulative survival rate at 18 months, MiVI 63.9% vs MaVI 55.5%; $P = 0.01$) (Figure 1A). Overall, 79 patients with MiVI died within 18 months after initial surgery (early death), whereas 118 patients survived longer than 18 months (long-term survival). Patients who died within 18 months after initial surgery were more likely to have multiple tumors (26.6% vs 13.6%; $P = 0.054$), lymph node metastasis (32.9% vs 16.0%; $P = 0.024$), and an R1 resection (31.6% vs 13.6%; $P = 0.003$) (Table 4). On multivariable analysis, lymph node metastasis (HR 2.6; 95%CI, 1.4-5.0; $P = 0.004$), R1 vs R0 margin (HR 2.4; 95%CI, 1.1-5.0; $P = 0.025$), and postoperative morbidity (HR 1.4; 95%CI, 1.0-2.0; $P = 0.05$) were independently associated with early death among patients with MiVI (Table 5). In contrast, among the 118 patients who survived longer than 18 months after initial surgery, only lymph node metastasis was correlated with late death (after 18 months) (HR 3.3; 95%CI, 1.5-7.0; $P = 0.002$) (Table 6).

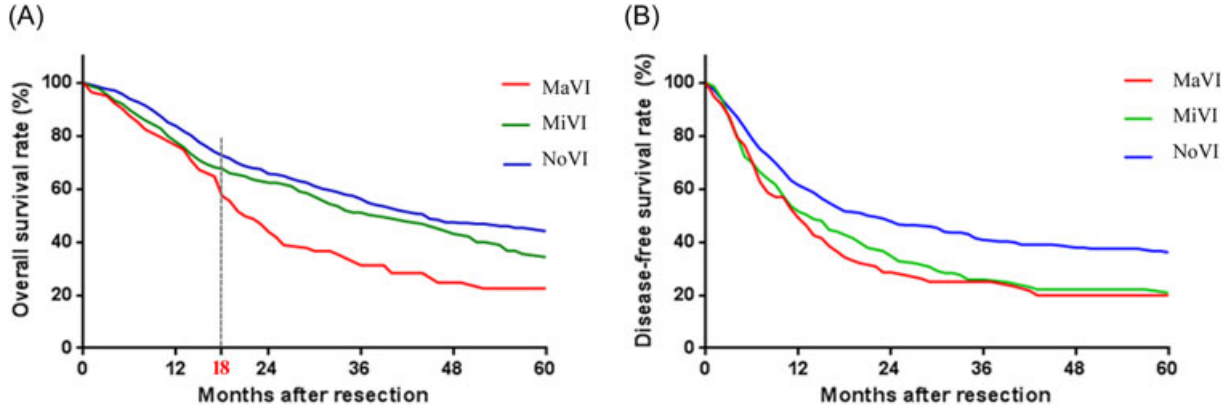

FIGURE 1 Overall (A) and disease-free survival (B) of patients undergoing curative-intent resection for intrahepatic cholangiocarcinoma stratified by vascular invasion status. NoVI, none vascular invasion; MiVI, microvascular invasion; MaVI, macrovascular invasion [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Risk factors for the overall survival of the whole cohort

	Univariate analysis		Multivariable analysis	
Variable	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**
Age ≥65, y	0.873	1.0 (0.9-1.2)		
Sex (M/F)	0.103	0.9 (0.7-1.0)		
Liver cirrhosis	0.877	1.0 (0.7-1.3)		
Tumor size >5 cm	<0.001	1.7 (1.4-2.1)	<0.001	1.6 (1.3-2.1)
Lymph node metastasis	<0.001	1.6 (1.3-1.9)	<0.001	2.0 (1.6-2.5)
Poorly to undifferentiated	<0.001	1.7 (1.4-2.1)	<0.001	1.7 (1.4-2.1)
Macrovascular invasion	<0.001	1.7 (1.3-2.1)	0.005	1.5 (1.1-1.9)
Microvascular invasion	0.379	1.1 (0.9-1.3)		
Multiple tumors	<0.001	1.9 (1.6-2. 3)	<0.001	1.7 (1.4-2.0)
R1 Margin	<0.001	1.8 (1.4-2.3)	<0.001	2.1 (1.6-2.8)
Adjuvant chemo- and radiotherapy	0.762	1.0 (0.9-1.2)		

Abbreviations: CI, confidence intervals; HR, hazard ratios .

TABLE 3 Risk factors for disease-free survival of the whole cohort

	Univariate analysis		Multivariable analysis	
Variable	***P* value**	**HR (95%CI)**	***P* value**	**HR (95%CI)**
Age ≥65 y	0.458	0.9 (0.8-1.1)		
Sex (M/F)	0.991	1.0 (0.9-1.2)		
Liver cirrhosis	0.524	0.9 (0.7-1.2)		
Tumor size >5 cm	<0.001	2.1 (1.7-2.5)	<0.001	2.0 (1.6-2.5)
Lymph node metastasis	0.093	1.2 (1.0-1.4)	0.005	1.3 (1.1-1.6)
Poorly to undifferentiated	<0.001	1.5 (1.2-1.8)	0.022	1.3 (1.0-1.6)
Macrovascular invasion	0.001	1.5 (1.2-1.8)	0.022	1.4 (1.0-1.8)
Microvascular invasion	0.002	1.4 (1.1-1.6)	<0.001	1.6 (1.3-2.0)
Multiple tumors	<0.001	1.8 (1.5-2. 2)	<0.001	1.6 (1.3-2.5)
R1 Margin	0.009	1.4 (1.1-1.8)	0.064	1.3 (1.0-1.7)
Adjuvant chemo and radiotherapy	<0.001	0.7 (0.6-0.9)	0.381	0.9 (0.8-1.1)

Abbreviations: CI, confidence intervals; HR, hazard ratios.

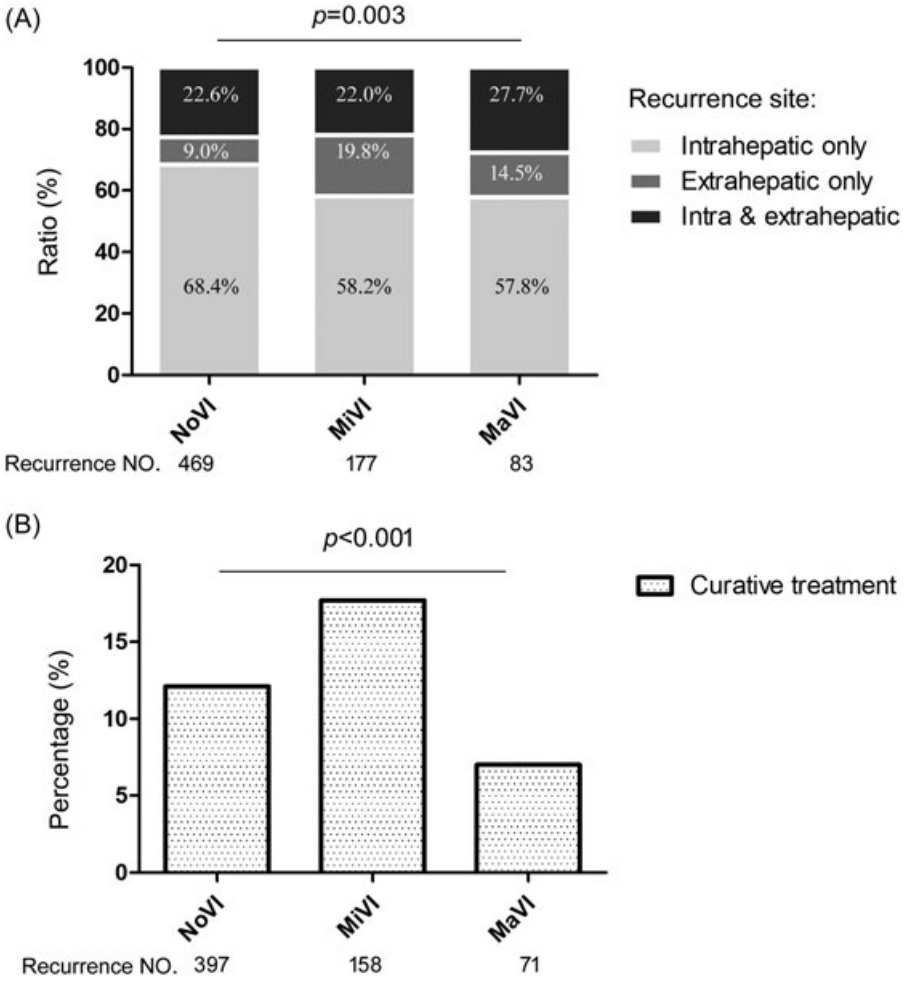

FIGURE 2 A, Recurrence pattern after curative-intent resection for intrahepatic cholangiocarcinoma among patients with no vascular invasion (NoVI), microvascular invasion (MiVI) or macrovascular invasion (MaVI). B, The proportion of patients receiving curative-intent treatments for recurrence in NoVI, MiVI and MaVI groups

4 | DISCUSSION

The AJCC 8th T classification incorporates vascular invasion as a staging parameter for ICC, yet fails to distinguish the impact of micro- vs macrovascular invasion.[9] Whether long-term survival of patients undergoing curative-intent surgery for ICC differs relative to micro- vs macro-vascular invasion has been poorly investigated. In the present multi-institutional study, both micro- and macrovascular invasion of ICC were associated with advanced tumor characteristics and stage. Compared with NoVI, the presence of MiVI increased the risk of tumor recurrence, yet was not associated with worse long-term survival after surgery. In contrast, MaVI was a strong indicator of both worse long-term and disease-free survival. The reason for these disparate results was likely done to a higher proportion of MiVI patients being candidates for repeat curative treatments at the time of recurrence compared with MaVI patients. Of note, early death among patients with MiVI was associated with tumor status (nodal metastasis), surgical technique (R1 margin), and postoperative complications. In contrast, the late death of patients was associated only with biological factors such as the presence of lymph node metastasis.

In the liver, small blood vessels are composed of an inner layer of endothelial cells surrounded by a basal membrane. When tumor cells in the liver have a sufficiently evolved phenotype, these cells can invade either the portal vein or hepatic vein branches leading to intrahepatic recurrence or systematic metastasis.[10] MiVI has been reported to be an independent predictor of tumor recurrence and mortality after resection or transplantation of HCC.[10-17] In turn, MiVI is commonly utilized in the pathological assessment and prognostic stratification of patients with HCC.[10-17] Data in the present study demonstrated that MiVI was an independent risk factor for tumor recurrence, but not long-term survival among patients with ICC. Specifically, patients with only MiVI had the same DFS compared with patients who had MaVI, as well as a comparable recurrence pattern (intrahepatic recurrence: 58.2% vs 57.8%). Interestingly, previous data had suggested that AJCC stage II HCC patients with MiVI had similar outcomes as patients with multiple tumors, implying that MiVI was a strong risk factor for intrahepatic recurrence.[13] In the present study, patients with ICC and histologically confirmed MiVI or MaVI had a higher incidence of perineural and biliary invasion, satellite lesions, advanced AJCC T stages, nodal metastasis, and poor differentiation. Given the association of vascular invasion with generally advanced disease, patients with MiVI in the pathological liver specimen should be closely surveilled for early detection and possible treatment of any recurrence. To this point, several studies have reported that

TABLE 4 Clinical and pathological characteristics of early dead (≤18 months) versus long-term survived (>18 months) patients with microvascular invasion

	Early death (n = 79)	Long-term survived (n = 118)	*P* value
Age, years	63 (52-71)	63 (56-70)	0.581
Men	47 (59.5%)	56 (47.5%)	0.127
BMI, kg/m^2	24.7 (22.1-29.2)	24.7 (22.5-28.1)	0.419
Tumor Size, cm	7.0 (5.0-8.7)	6.5 (4.0-9.5)	0.576
Multiple lesions (≥2)	21 (26.6%)	16 (13.6%)	0.054
Perineural invasion	30 (38.0%)	36 (30.5%)	0.323
Direct invasion of adjacent organs	4 (5.1%)	5 (4.2%)	0.997
Biliary invasion	16 (20.3%)	22 (18.6%)	0.676
Satellite lesions	29 (36.7%)	28 (23.7%)	0.063
AJCC tumour category			0.455
T1–2	44 (55.7%)	55 (46.6%)	
T3–4	23 (29.1%)	23 (19.5%)	
Missing	12 (15.2%)	40 (33.9%)	
AJCC node category			0.024
N0	28 (35.4%)	46 (46.0%)	
N1–2	26 (32.9%)	16 (16.0%)	
Nx	20 (25.3%)	38 (38.0%)	
Histological grade			0.105
Well to moderately differentiated	49 (62.0%)	78 (66.1%)	
Poorly to undifferentiated	22 (27.8%)	18 (15.3%)	
Missing	8 (10.1%)	22 (18.6%)	
R0 resection	54 (68.4%)	102 (86.4%)	0.003
Lymphadenectomy	49 (62.0%)	63 (53.4%)	0.455
Intraoperative blood loss, mL	500 (250-1300)	500 (300-763)	0.613
Operation time, min	300 (192-411)	290 (203-430)	0.716
Adjuvant chemo- and radiotherapy	31 (39.2%)	49 (41.5%)	0.749

Abbreviation: AJCC, American Joint Committee on Cancer.

liver-directed therapy for recurrences, such as surgical resection, transarterial chemoembolization, and radiofrequency ablation, might improve the prognosis of patients with recurrent ICC.[22-24] In addition, although the effect of adjuvant chemotherapy on the prognosis of ICC patients remains debatable, several studies have demonstrated potential survival benefits of adjuvant chemotherapy among "high-risk" patients with advanced tumor characteristics, such as nodal metastasis, advanced stages, or an inadequate margin.[1,25,26] As such, patients with MiVI should similarly be considered for appropriate adjuvant therapy.

While DFS was comparable among patients with MiVI and MaVI, median OS was longer among patients with MiVI (39.0 vs 21.0 months). In fact, despite differences in DFS, OS of patients with MiVI was even comparable to the OS of patients who had NoVI (39.0 vs 45.0 months). While the reasons for these differences were undoubtedly multifactorial, these findings can be explained in part by the fact that patients with MiVI had a higher utilization of curative treatment of recurrences than patients with MaVI (17.7% vs 7.0%). While data on the extent/burden of tumor recurrence were not available, the higher utilization of repeat curative-intent surgery among patients with MiVI strongly implied a less aggressive phenotype of intrahepatic-only recurrence among patients with MiVI vs MaVI. To this point, median OS after the first recurrence among patients with MiVI was more than double that of patients with MaVI (17.0 vs 8.0 months).

In examining survival, patients with MiVI had a comparable prognosis as patients with MaVI within the first 1 to 2 years after surgery yet diverged at 18 to 24 months. Previous work from our group had suggested that the timing of early vs late recurrence among patients with ICC could be defined empirically using a cut-off of about 2 years.[6] In addition, among patients who did recur, the overwhelming majority recurred early. Similarly, in the present study, we were able to identify two prognostic cohorts among patients who had MiVI. In particular, there was a subset of patients who experienced early recurrence and death within the first 18 to 24 months after surgery. Interestingly, on multivariable analysis, factors associated with early mortality included multiple tumors (26.6% vs 13.6%; $P = 0.054$), lymph node metastasis (32.9% vs 16.0%; $P = 0.024$), and an R1 resection (31.6% vs 13.6%; $P = 0.003$).[5,27-31] In contrast, among patients who were late survivors, the only factor associated with prognosis was lymph node metastasis, as patients with the nodal disease had a three-fold increased risk of late death (HR 3.3; 95% CI 1.5-7.0; $P = 0.002$). Lymph node status has previously been documented as one of the strongest prognostic factors associated with outcomes among patients with ICC.[32-38] The present study highlights how lymph node status remained a strong indicator of prognosis even among patients with other risk factors such as MiVI. As such, routine lymphadenectomy to assess the nodal basin should be performed at the time of surgery to obtain important prognostic information, guide adjuvant therapy recommendations, as well as possibly prevent hilar nodal recurrence.[34,39-42]

Several limitations need to be considered when interpreting the present study. While the multicenter nature of the study undoubtedly increased sample size and analytical power, selection bias and variation in treatment strategies were possible. For example, patient selection for surgical resection has evolved over time and surgical approaches may have varied across the different centers. In addition, the diagnosis of MiVI was largely dependent on sample collection and histological examination. Therefore, it was possible that some variability in reporting of MiVI may have occurred, although this was likely low as the participating hospitals were major HPB centers with expertise in hepatopathology.

TABLE 5 Risk factors for early death (≤18 months) of patients undergoing curative-intent resection for intrahepatic cholangiocarcinoma with microvascular invasion

	Univariate analysis		Multivariable analysis	
Variable	*P* value	OR (95%CI)	*P* value	OR (95%CI)
Age ≥65 y	0.829	1.1 (0.6-1.9)		
Sex (M/F)	0.085	0.6 (0.4-1.1)		
Tumor size >5 cm	0.207	1.6 (0.8-3.1)		
Lymph node metastasis	0.001	2.9 (1.6-5.2)	0.004	2.6 (1.4-5.0)
Poorly to undifferentiated	0.099	1.8 (0.9-3.7)		
Multiple tumors	0.074	2.0 (0.9-4. 0)		
R1 margin	0.002	3.0 (1.5-6.0)	0.025	2.4 (1.1-5.0)
Postoperative morbidity	0.040	1.4 (1.0-2.0)	0.050	1.4 (1.0-2.0)
Adjuvant chemo- and radiotherapy	0.090	0.7 (0.4-1.1)		

Abbreviations: CI, confidence intervals; OR, odds ratio.

TABLE 6 Risk factors for the overall survival of patients with MiVI who survive longer than 18 months

	Univariate analysis	
Variable	*P* value	OR (95%CI)
Age ≥65 y	0.812	1.1 (0.5-2.3)
Sex (M/F)	0.357	0.7 (0.3-1.5)
Tumor size >5 cm	0.657	1.2 (0.5-2.8)
Lymph node metastasis	0.002	3.3 (1.5-7.0)
Poorly to undifferentiated	0.477	1.5 (0.5-4.1)
Multiple tumors	0.443	1.5 (0.5-4. 5)
R1 margin	0.505	0.7 (0.2-2.1)
Postoperative morbidity	0.700	0.9 (0.6-1.5)
Adjuvant chemo- and radiotherapy	0.542	0.8 (0.5-1.5)

Abbreviations: CI, confidence intervals; OR, odds ratio.

In conclusion, among patients undergoing curative resection for ICC, roughly one out of five patients had MiVI on histological examination, while one out of ten patients had the macrovascular invasion. MiVI was associated with advanced tumor characteristics, and thus a higher risk of tumor recurrence. Risk of early death among patients with MiVI was associated with tumor and surgical factors, while the risk of late death was largely impacted by lymph node status. MiVI status should be routinely documented in the pathology report of patients undergoing resection of ICC as these data have prognostic and possibly treatment-related implications.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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